Louisiana Chemical Association Comments on

Draft IRIS Toxicological Review of Formaldehyde (Inhalation)

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Background on Formaldehyde

Formaldehyde is a ubiquitous compound found in many living things and is also manufactured for a number of applications. Formaldehyde is widely used in plywood adhesives, abrasive materials, insulation, pesticides, and embalming fluids. It is also used in plastics and coatings, textile finishing, chemical manufacturing, and as a disinfectant and preservative. Formaldehyde is used in consumer goods to deter spoilage caused by microbial contamination. It has been used as a preservative in household cleaning agents, dishwashing liquids, fabric softeners, shoe-care agents, car shampoos and waxes, and carpet-cleaning agents (ATSDR, 1999). It is also a byproduct of combustion of plant materials (including tobacco), wood, gasoline, natural gas and other fuels.

Comments

Public Comment Period

The Louisiana Chemical Association ("LCA") previously requested that the Environmental Protection Agency ("EPA") extend the comment period on the Draft Review for no less than 60 additional days. Additionally, LCA requested that EPA hold a public listening session (virtually or in-person) with a comment period extending at least 30 days after the session. (LCA, May 25,2022). Notably, many other industrial and commercial entities made similar requests, which demonstrates the universal need for more time to review and to digest the lengthy EPA documents and the supporting information. As of the date of this submittal, EPA has not granted an extension or held a public listening session.

LCA considers the 60-day public comment period woefully inadequate to allow thorough review the voluminous Draft Review documents (surpassing well over 2,000 pages in total) and the many studies and government reports relating to its contents, let alone time to prepare informed and complete comments for submission to EPA. The 60-day period allows for only a preliminary review and commentary and thus undermines the transparency of and confidence in EPA's review process. LCA urges EPA to continue to take comments even after the current June 13, 2022 deadline.

Upper Respiratory Tract Cancers

The classification of "evidence demonstrates" that formaldehyde causes nasopharyngeal cancer (NPC) and sinonasal cancers is not fully supported and should be reevaluated based on the growing amount of information which argues against a causal association. Based on EPA guidelines (Table 8 of EPA, 2022a), the classifications of "evidence indicates" is more appropriate given the conflicting and inconsistent findings in human epidemiological studies, the indications of chance, bias and confounders in key positive epidemiological studies, and the stronger but limited evidence in high exposure rat studies.

- The Beane Freeman et al., 2013 update of the 2009 NCI Cohort, a key epidemiological study relied upon in the Draft Review and containing data which was designated as "high confidence" revealed:

    - For all cancer, solid tumors and lung cancer, standardized mortality rates (SMRs) among exposed workers were elevated, but internal analyses, which better control for external confounders, revealed no positive associations with formaldehyde exposure.

    - A decreased rate ratio (RR) rather than an increased RR for death from all causes was observed for those in the highest category of formaldehyde exposure as measured by peak, average intensity, and cumulative exposure.

    - For cancer of the nose and nasal sinus, "no apparent association with any metric of formaldehyde exposure" was observed.

    - There was "an increased RR of nasopharyngeal cancer in the highest categories of formaldehyde exposure", but "there were also elevations in the risk estimates in the non-exposed categories for all metrics of exposure". This finding suggests that the increases seen could be due to chance or confounding factors.

    - In the 10-year follow-up period included in the 2013 update, there was one death from NPC observed which was lower than 1.2 deaths expected. This death occurred in the lowest category of peak, average intensity, and cumulative formaldehyde exposure.

    - The conclusion of Beane Freeman et al., 2013 was that "this update continues to **suggest** (emphasis added) a link between formaldehyde exposure and nasopharyngeal cancer". Suggestion of a link does not equate to causality.

- Marsh et al. (2014 and 2016) performed a critical review of Beane Freeman et al. (2013) and re-analyzed the NCI cohort mortality data used in that study and presented evidence that argues against an association between formaldehyde and NPC mortality:

    - A single, lower than expected, NPC death occurred in the lowest formaldehyde exposure categories.

    - The overall SMR for NPC among all formaldehyde exposed workers was no longer statistically significant.

    - The SMR for NPC among formaldehyde exposed workers was now consistent with the corresponding SMR for all unexposed workers as the 95% confidence interval for the exposed workers was entirely contained within the confidence interval for the unexposed workers.

    - There is no meaningful difference in the RRs for NPC mortality between the unexposed and formaldehyde exposed groups.

    - The conclusion of an association between formaldehyde and NPC mortality risk was driven by the large, statistically significant excess in NPC mortality risk in one (Plant 1) out of the ten plants included in the cohort study. This interaction structure between plant group (Plant 1 and Plants 2-10) and formaldehyde exposure was not accounted for in the Beane Freeman et al. (2013) study and is a significant confounding factor.

    - Notably, the Marsh et al. Plant 1 study revealed considerable evidence that the overall NPC mortality excess at Plant 1 was not related to formaldehyde exposure, but rather reflected exposure to other risk factors associated with employment in the local ferrous and non-ferrous metal industries. In fact, Marsh et al. (2016) reported a large statistically significant, local rate-based elevated NPC SMR among formaldehyde exposed workers in Plant 1, but an 18% deficit in NPC deaths in the exposed workers of the other nine plants.

    - The Beane Freeman et al., 2013 trend tests based on all unexposed and exposed categories were not statistically significant, which suggests that NPC mortality excesses in the unexposed are due to chance or the presence of external confounding factors which is consistent with the findings reported by Marsh et al. for Plant 1 (see previous bullet).

- Marsh et al. (2014) concluded that an association between formaldehyde exposure and NPC mortality was not consistent with the available data in the Beane Freeman et al. (2013) update or other cohort studies and research findings.

- Marsh et al. (2016) concluded that their re-analysis of the Beane Freeman et al. (2013) data provided little or no evidence to support the conclusion that the update continues to suggest an association between formaldehyde exposure and mortality from NPC.

- Epidemiology studies of upper respiratory tract cancers provide inconsistent results.

  - As stated in Beane Freeman et al., 2013:

    - "Several other epidemiologic studies independent of this cohort have reported an association between NPC and formaldehyde exposure [Vaughan et al., 1986b, 2000; Roush et al., 1987; Hayes et al., 1990; Partanen, 1993; West et al., 1993; Hildesheim et al., 2001], but some have not [Walrath and Fraumeni, 1983; Coggon et al., 2003; Pinkerton et al., 2004]."
    - "Of the positive studies, one showed an increase in squamous and unspecified epithelial cell carcinomas with increasing formaldehyde exposure, but not with undifferentiated or non-keratinizing carcinomas of the nasopharynx [Vaughan et al., 2000]".
    - Included in the negative group are "two large industrial cohort studies of 14,014 chemical workers in the United Kingdom and 11,039 workers in the garment industry in the United States".

  - Additional studies not cited by Beane Freeman et al. (2013) above add to the negative group which dispute an association between formaldehyde exposure and NPC and include, but are not limited to:

    - Coggon et al. (2014) extended follow-up of a cohort of 14,008 chemical workers at six factories in England and Wales, covering the period 1941–2012, and demonstrated that nested case-control analyses of 115 men with upper airways cancer (including one nasopharyngeal cancer) indicated no elevations of risk in the highest exposure category (high exposure for ≥1 year). The authors concluded that their study results provided no support for an increased hazard of nasopharyngeal carcinoma, or other upper airway tumors from formaldehyde exposure.
    - Protano et al. (2021) synthesized the results of epidemiological studies of formaldehyde exposure in occupational settings carried out in the last 20

years. The authors concluded that the results showed a weak association with nasopharyngeal cancer, and that the evidence of correlation between formaldehyde occupational exposure and the occurrence of cancer in general is limited.

- Animal studies provide evidence of nasal cancers only following inhalation exposure to high concentrations of formaldehyde.

    - The only clear association between formaldehyde exposure and carcinogenicity arises from chronic inhalation studies in rats which report tumors only in the nasal passages of rats exposed to $\geq$ 6 ppm formaldehyde (Thompson et al., 2020; Swenberg et al., 1980; Swenberg et al., 1983).

    - Findings in Wistar rats are unclear as compared to Fischer 344 and Sprague Dawley (EPA, 2022a).

    - Inhalation studies in mice have shown limited evidence of nasal carcinogenicity possibly due to a lower exposure dose caused by irritant-induced reflex bradypnea (Swenberg et al., 1983).

    - Hamsters appear to be more resistant to formaldehyde as chronic exposure up to 10 ppm did not induce nasal tumors (Thompson et al., 2020).

Myeloid Leukemia

The classification of "evidence demonstrates" that formaldehyde causes myeloid leukemia is not supported and should be reevaluated based on the growing amount of information which argues against a causal association. Based on EPA guidelines (Table 8 of EPA, 2022a), the classification of "evidence suggests" is more appropriate given the conflicting and inconsistent findings in human epidemiological studies, the indications of chance, bias and confounders in key positive epidemiological studies, the consistent lack of statistically significant associations, negative animal studies, and the lack of mechanistic evidence supporting a mode of action.

- Beane Freeman et al. (2009) reported statistically nonsignificant associations between formaldehyde and myeloid leukemia in the NCI workers cohort. The authors equivocally concluded that findings "suggest a possible link between formaldehyde exposure and lymphohematopoietic malignancies, particularly myeloid leukemia". They also acknowledged that the observed findings could be due to chance.

- In its June 2, 2010 comments to the initial 2010 Draft Toxicological Review of Formaldehyde, the Texas Commission on Environmental Quality (TCEQ) disagreed with EPA that human epidemiological evidence was sufficient to conclude a causal association between formaldehyde exposure, leukemia, and lymphohematopoietic cancers as a group considering:

    - the inconsistency of the associations;

    - the weakness of the associations as demonstrated by the RRs and confidence intervals in Beane Freeman et al. (2009), the principal study used by EPA; and

    - the biological implausibility of formaldehyde-induced genotoxic effects at sites beyond the portal of entry.

- The inconsistency and weakness of associations and biological implausibility noted by TCEQ remain valid considerations for discounting the sufficiency of evidence for a causal association between formaldehyde and myeloid leukemia in the current 2022 Draft Review, which also relies on the Beane Freeman et al. (2009) study.

- In its January 5, 2022 comments on the Draft Review, the U.S. Office of Management and Budget (OMB) expressed concern with EPA's judgement of "evidence demonstrates" for myeloid leukemia "given the inconsistencies in the epidemiological data and the lack of proposed MOA".

    - OMB further stated that "(c)laiming "evidence demonstrates" while the confidence in the unit risk estimate is low and the data are limited may result in an overly conservative appreciation of the degree of hazard for myeloid leukemia, particularly considering no mode of action (MOA) has been established to explain how formaldehyde inhalation can cause myeloid leukemia, a disease that results from systemic exposure. The mechanistic information considered by EPA may support associations with local, route-of-exposure, tumors associated with epithelial cells, but does not support the tumorigenesis or carcinogenesis of disease related to systemic exposures."

    - OMB suggested that "evidence demonstrates" be downgraded to "The evidence indicates that formaldehyde is likely associated with an increased risk...".

- EPA (2022a) states that "the database was insufficient to support the evaluation or development of any specific MOA" for myeloid leukemia.

- Gentry et al. (2020) reviewed available mechanistic data for leukemia and concluded that "(t)he integration of all the available evidence clearly highlights the limited amount of data that support any of the postulated MOAs and demonstrates a significant amount of research supporting the null hypothesis that there is no causal association between formaldehyde inhalation exposure and leukemia. These analyses result in a lack of confidence in any of the postulated MOAs, increasing confidence in the conclusion that there is a lack of biological plausibility for a causal association between formaldehyde inhalation exposure and leukemia."

- EPA (2022a) states that "positive associations with leukemia have not been reported in rodent studies" and there was "indeterminate evidence as to whether formaldehyde exposure might be capable of causing leukemia or lymphoma in animals based on the currently available evidence".

- Following analysis of the NCI workers cohort, Checkoway et al. (2015) reported that acute myeloid leukemia (AML), the type of leukemia with known chemical risk factors, was unrelated to cumulative formaldehyde exposure, or even exposures to peak exposure to formaldehyde. The authors concluded that the findings of their re-analysis of the NCI cohort data "do not support the hypothesis that formaldehyde is a cause of AML".

- Mundt et al. (2017) reanalyzed study data from Zhang et al. (2010), a very influential but never replicated study that reported aneuploidy (a chromosome abnormality) in the blood of formaldehyde workers and suggested this was indication of myeloid leukemia risk. Mundt et al. (2017) concluded from their reanalysis of the original Zhang data that "among formaldehyde-exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy". Methodological problems of the Zhang et al. (2010) study are presented by Gentry et al. (2013) and Mundt et al. (2017).

- Meyers et al. (2013), an update of the cohort study of garment workers, concluded, "We continue to see limited evidence of an association between formaldehyde and leukemia. However, the extended follow-up did not strengthen previously observed associations."

- Coggon et al. (2014) extended follow-up of a cohort of 14,008 chemical workers at six factories in England and Wales, covering the period 1941–2012, and demonstrated that "(n)ested case-control analyses of 115 men with upper airways cancer (including one nasopharyngeal cancer), 92 with leukaemia, and 45 with myeloid leukaemia indicated no elevations of risk in the highest exposure category (high exposure for ≥1 year)....Our results provide no support for a hazard of myeloid leukaemia, nasopharyngeal carcinoma

or other upper airways tumours from formaldehyde, and indicate that any excess risk of these cancers, even from relatively high exposures, is at most small".

- Protano et al. (2021) synthesized the results of epidemiological studies of formaldehyde exposure in occupational settings carried out in the last 20 years. The authors concluded that the results showed a weak association with leukemia, and that the evidence of correlation between formaldehyde occupational exposure and the occurrence of cancer in general is limited.

- Allegra et al. (2019) performed a literature review of 81 studies and concluded that "findings from the review of the literature do not support the hypothesis that formaldehyde is a cause of myeloid leukemia".

- Thompson et al. (2020) concluded that "(a) statistical association of formaldehyde exposure with leukemia has not been consistently observed in retrospective epidemiology studies.

Toxicity Criteria Development and Plausibility

Inhalation Unit Risk for NPC

The inhalation unit risk (IUR) for NPC was developed using the NCI cohort study (Beane Freeman et al., 2013) as "it is the only one with sufficient individual exposure data for dose response modeling" (EPA, 2022a). The weak and inconsistent associations, methodological issues, and external confounders of the study are mentioned above and are discussed in detail in the cited references.

The IUR for NPC is based on a mutagenic mode of action (MOA) which assumes a linear non-threshold (LNT) dose response (EPA, 2005). The available science does not support the use of a LNT assumption to estimate toxicity criteria for formaldehyde, a chemical which EPA acknowledges has a mixed MOA and evidence of non-linear dose response relationships (EPA, 2022a & b). Some of the available evidence of a mixed MOA and non-linearity is presented below:

- EPA (2002a) states, "(t)he highly curvilinear and steeply increasing dose-responses for DPX formation and cell proliferation, concomitant with the highly nonlinear observed tumor incidence in the F344 rat, have led to mechanistic arguments that formaldehyde's nasal carcinogenicity arises only in response to significant cytotoxicity-induced regenerative cell proliferation (Conolly et al., 2002; Morgan, 1997)".

- Human (Beane Freeman et al. 2013) and animal (Kerns et al., 1983; Monticello et al., 1996) studies have indicated nonlinear dose-response relationships for the risk of squamous cell nasal cancer.

- Formaldehyde induces nonlinear, concentration-related increases in nasal epithelial cell proliferation and squamous cell carcinomas (SCC) in rats (Monticello et al., 1996).

- Lu et al. (2010) determined that in rats, formaldehyde induces exogenous DNA adducts in a highly non-linear fashion. Formation of DNA adducts is a key event in mutagenesis and carcinogenesis.

- Tumor induction by formaldehyde "is driven by sustained cytotoxicity and cell proliferation while genetic changes are secondary (McGregor et al., 2006). Therefore a threshold can be established for formaldehyde concentrations not leading to such sustained cell proliferation and histopathological alterations" (SCOEL, 2016).

- There are exposure concentrations below which there are no detectable biomarkers of exposure in rats (Thompson et al., 2020).

- Data in rats do not indicate genotoxic or mutagenic responses up to 15 ppm (Thompson et al., 2020).

- Formaldehyde is considered a "genotoxic carcinogen for which a practical threshold is supported" (SCOEL, 2016).

- Thompson et al. (2020), a comprehensive review and update of the MOA for nasal tumors, states, "(t)hese new data, together with the previous data, indicate that toxicity criteria for formaldehyde estimated with linear approaches is not supported by the available science" and that the low-dose extrapolation used by EPA based on a LNT model is "likely inaccurate for many chemical carcinogens, but it seems particularly inapplicable to formaldehyde".

EPA applied age-dependent adjustment factors (ADAFs) to develop the UR for NPC which is typically done for chemicals with a mutagenic MOA. However, EPA acknowledges that the carcinogenicity of formaldehyde can be attributed only in part to a mutagenic MOA. The scientific defensibility of applying ADAFs to the toxicity criteria for a chemical known to have a multi-faceted MOA, non-linear dose-response relationships, and an effect threshold is questionable.

The 2022 NPC IUR is 1.1×10^{-5} per $\mu g / m^3$ (1.1 excess cancer cases are expected to develop per 100,000 people if exposed daily for a lifetime to 1 $\mu g/m^3$). The overall confidence level of EPA in

the NPC IUR is medium based largely on "the small number of cases that contributed to the statistical analysis and resulting imprecision in modeling the shape of the dose-response curve" (EPA, 2022a). The 2022 NPC IUR is similar to the 1991 IUR of 1.3×10^{-5} based on nasal squamous cell carcinomas in F344 rats (EPA, 2022a).

Inhalation Unit Risk for Myeloid Leukemia

EPA was compelled to develop a IUR estimate because of its judgement that the available "evidence demonstrates" that formaldehyde causes myeloid leukemia. As discussed above, LCA and other groups and scientists disagree with this designation of causality due to weak or absent causal associations, inconsistent findings, no established mode of action, etc. The methodology used by EPA to develop the IUR for myeloid leukemia further demonstrates why "evidence demonstrates" is inappropriate:

- "The quantitative analyses of myeloid leukemia are based on results from the latest follow-up of the NCI cohort of industrial workers exposed to formaldehyde (Beane Freeman et al., 2009). Although no association was indicated for cumulative exposure and myeloid leukemia in this study, the combination of myeloid leukemia and other/unspecified leukemia was marginally associated (p = 0.1) with cumulative formaldehyde exposure" (EPA 2022a).

- EPA (2022a) states, "there are insufficient data to establish the MOA for formaldehyde-induced myeloid leukemia; thus, linear low-dose extrapolation was performed as the default approach, in accordance with EPA's cancer guidelines (U.S. EPA, 2005a)". The issues regarding application of a LNT model are discussed in the IUR for NPC section above.

- The development of a unit risk for myeloid leukemia did not assume a mutagenic MOA because "there is no knowledge as to whether a mutagenic MOA might be operative for formaldehyde-induced myeloid leukemia" (EPA, 2022a). Therefore, no adjustments for increased early-life susceptibility (i.e., application of age-dependent adjustment factors) were made for myeloid leukemia.

- EPA expressed low confidence in the unit risk estimate for myeloid leukemia (EPA, 2022a).

Because of the insufficient human and animal data base, EPA used exposure data for myeloid leukemia plus other/unspecified leukemias (which may include cases of myeloid leukemia but does include cases of non-myeloid leukemias) to develop the IUR. Due to the lack of data showing causal associations, EPA used exposure data that did not show an association with formaldehyde exposure. Because mechanistic data are insufficient to determine a MOA for formaldehyde induction of myeloid leukemia if it occurs, EPA used a default linear low-dose extrapolation, the shortcomings of which were presented under the discussion of the IUR for NPC. EPA (2002a)

states that it used "an innovative approach" *i.e.*, one not yet subject to review and approval by the scientific community, to derive and present potential unit risk estimates for myeloid leukemia.

EPA has developed an IUR for myeloid leukemia which seems scientifically indefensible and in which the Agency admits it has low confidence.

Although the medium confidence NPC IUR was selected by EPA over the low confidence myeloid leukemia IUR, LCA supports and reminds EPA of the comment made by TCEQ (2010):

> "Given their important role in the protection of public health, EPA regulatory risk assessors have a duty to perform the most scientifically-defensible assessments possible while giving careful and due consideration to comments and recommendations from other regulatory agencies, the public, external experts, stakeholders, etc. Although regulatory risk assessors have a penchant for erring on the side of health-protectiveness and conservative defaults, if erring on the side of conservatism significantly overestimates risk or hazard and is not fully justified, then harm to public health may result from diverting public, industry, and government attention and resources away from chemicals which may represent more of a public health risk at environmental levels."

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